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Introduction

The extracellular matrix (ECM) is a complex structural entity surrounding and supporting cells that are found within mammalian tissues. The ECM is often referred to as the **connective tissue**. The ECM is composed of 3 major classes of biomolecules:

1. **Structural proteins:** collagen and elastin.

2. **Specialized proteins:** e.g. fibrillin, fibronectin, and laminin.

3. **Proteoglycans:** these are composed of a protein core to which is attached long chains of repeating disaccharide units termed of glycosaminoglycans (GAGs) forming extremely complex high molecular weight components of the ECM. Proteoglycans are covered in the section on Glycosaminoglycans and Proteoglycans.

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Collagens

Collagens are the most abundant proteins found in the animal kingdom. It is the major protein comprising the ECM. There are at least 12 types of collagen. Types I, II and III are the most abundant and form fibrils of similar structure. Type IV collagen forms a two-dimensional reticulum and is a major component of the basal lamina. Collagens are predominantly synthesized by fibroblasts but epithelial cells also synthesize these proteins.

The fundamental higher order structure of collagens is a long and thin diameter rod-like protein. Type I collagen for instance is 300nm long, 1.5nm in diameter and consists of 3 coiled subunits composed of two α1(I) chains and one α2(I) chain. Each chain consists of 1050 amino acids wound around each other in a characteristic right-handed triple helix. There are 3 amino acids per turn of the helix and every third amino acid is a G. Collagens are also rich in proline and hydroxyproline. The bulky pyrollidone rings of proline reside on the outside of the

triple helix.

Lateral interactions of triple helices of collagens result in the formation of fibrils roughly 50nm diameter. The packing of collagen is such that adjacent molecules are displaced approximately 1/4 of their length (67nm). This staggered array produces a striated effect that can be seen in the electron microscope.

Collagens are synthesized as longer precursor proteins called **procollagens**. Type I procollagen contains an additional 150 amino acids at the N-terminus and 250 at the C-terminus. These pro-domains are globular and form multiple intrachain disulfide bonds. The disulfides stabilize the proprotein allowing the triple helical section to form.

Collagen fibers begin to assemble in the ER and Golgi complexes. The signal sequence is removed and numerous modifications take place in th ecollagen chains. Specific proline residues are hydroxylated by ***prolyl 4-hydroxylase*** and ***prolyl 3-hydroxylase***. Specific lysine residues also are hydroxylated *by* ***lysyl hydroxylase***. Both prolyl hydraoxylases are absolutely dependent upon vitamin C as co-factor. Glycosylations of the O-linked type also occurs during Golgi transit. Following completion of processing the procollagens are secreted into the extracellular space where extracellular enzymes remove the pro-domains. The collagen molecules then polymerize to form collagen fibrils. Accompanying fibril formation is the oxidation of certain lysine residues by the extracellular enzyme ***lysyl oxidase*** foming reactive aldehydes. These reactive aldehydes form specific cross-links between two chains thereby, stabilizing the staggered array of the collagens in the fibril.

Types of Collagen

Types	Chain Composition	Structural Details	Localization
I	$[\alpha1(I)]_2[\alpha(I)]$	300nm, 67nm banded fibrils	skin, tendon, bone, etc.
II	$[\alpha1(II)]_3$	300nm, small 67nm fibrils	cartilage, vitreous humor
III	$[\alpha1(III)]_3$	300nm, small 67nm fibrils	skin, muscle, frequently with type I
IV	$[\alpha1(IV)_2[\alpha2(IV)]$	390nm C-term globular domain, nonfibrillar	all basal lamina
V	$[\alpha1(V)][\alpha2(V)][\alpha3(V)]$	390nm N-term globular domain, small fibers	most interstitial tissue, assoc. with type I
VI	$[\alpha1(VI)][\alpha2(VI)][\alpha3(VI)]$	150nm, N+C term. globular domains, microfibrils, 100nm banded fibrils	most interstitial tissue, assoc. with type I

VII	$[\alpha1(VII)]_3$	450nm, dimer	epithelia
VIII	$[\alpha1(VIII)]_3$	?, ?	some endothelial cells
IX	[α1(IX)][α2(IX)][α3(IX)]	200nm, N-term. globular domain, bound proteoglycan	cartilage, assoc. with type II
X	$[\alpha1(X)]_3$	150nm, C-term. globular domain	hypertrophic and mineralizing cartilage
XI	[α1(XI)][α2(XI)][α3(XI)]	300nm, small fibers	cartilage
XII	α1(XII)	?, ?	interacts with types I and III

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Clinical Significance of Collagen Disorders

Collagens are the most abundant proteins in the body. Alterations in collagen structure resulting from abnormal genes or abnormal processing of collagen proteins results in numerous diseases, e.g. Larsen syndrome, **scurvy**, osteogenesis imperfecta and Ehlers-Danlos syndrome.

Ehlers-Danlos syndrome is actually the name associated with at least ten distinct disorders that are biochemically and clinically distinct yet all manifest structural weakness in connective tissue as a result of defects in the structure of collagens. **Osteogenesis imperfecta** also encompasses more than one disorder. At least four biochemically and clinically distinguishable disorders have been identified all of which are characterized by multiple fractures and resultant bone deformities.

Marfan's syndrome manifests itself as a disorder of the connective tissue and was believed to be the result of abnormal collagens. However, recent evidence has shown that Marfan's results from mutations in the extracellular protein, **fibrillin**, which is an integral constituent of the non-collagenous microfibrils of the extracellular matrix.

Disorder	Collagen Defect	Symptomology
Ehlers-Danlos IV	decrease in type III	arterial, intestinal and uterine rupture, thin easily bruised skin
Ehlers-Danlos V	decreased cross-linking	skin and joint hyperextensibility
Ehlers-Danlos VI	decreased hydroxylysine	poor wound healing, musculo-skeletal deformities, skin and joint hyperextensibility

Ehlers-Danlos VII	N-terminal pro-peptide not removed	easily bruised skin, hip dislocations, hyperextensibility
Oseteogenesis imperfecta	decrease in type I	blue sclerae, bone deformities
Scurvy	decreased hydroxyproline	poor wound healing, deficient growth, capillary weakness

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Fibronectin

The role of fibronectins is to attach cells to a variety of extracellular matrices. Fibronectin attaches cells to all matrices except type IV that involves laminin as the adhesive molecule. Fibronectins are dimers of 2 similar peptides. Each chain is 60-70nm long and 2-3nm thick. At least 20 different fibronectin chains have been identified that arise by alternative RNA splicing of the primary transcript from a single fibronectin gene.

Fibronectins contain at least 6 tightly folded domains each with a high affinity for a different substrate such as heparan sulfate, collagen (separate domains for types I, II and III), fibrin and cell-surface receptors. The cell-surface receptor-binding domain contains a consensus amino acid sequence, **RGDS**.

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Laminin

All basal laminae contain a common set of proteins and GAGs. These **are type IV collagen**, **heparan sulfate proteoglycans**, **entactin** and **laminin**. The basal lamina is often refered to as the **type IV matrix**. Each of the components of the basal lamina is synthesized by the cells that rest upon it. Laminin anchors cell surfaces to the basal lamina.

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Representative matrix types produced by vertebrate cells

Collagen	Anchor	Proteoglycan	Cell-Surface Receptor	Cells
I	fibronectin	chondroitin and dermatan sulfates	integrin	fibroblasts
II	fibronectin	chondroitin sulfate	integrin	chondrocytes

III	fibronectin	heparan sulfate and heparin	integrin	quiescent hepatocytes, epithelial; assoc. fibroblasts
IV	laminin	heparan sulfate and heparin	laminin receptors	all epithelial cells, endothelial cells, regenerating hepatocytes
V	fibronectin	heparan sulfate and heparin	integrin	quiescent fibroblasts
VI	fibronectin	heparan sulfate	litegrin	quiescent fibroblasts

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